SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

HIDROCOL, 4000000 IU/ml solution for use in drinking water/milk

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:
Colistin (as sulfate) 4000000 IU

Excipients:
Benzyl alcohol (E1519) 0.010 ml

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for use in drinking water/milk
A brown –orange solution

4. CLINICAL PARTICULARS

4.1 Target species

Cattle (calves), sheep (lambs), pigs, chickens and turkeys.

4.2 Indications for use, specifying the target species

Treatment and metaphylaxis of enteric infections caused by non-invasive E. *Coli*, susceptible to colistin.
In the case of metaphylaxis, the presence of the disease in the group / flock must be established before the product is used.

4.3 Contraindications

Do not use in cases of hypersensitivity to colistin sulfate or to any of the excipients.
Do not use in cases of resistance to polymyxins.
Do not use in horses, particularly in foals, since colistin sulfate, due to a shift in the gastrointestinal microflora balance could lead to the development of antimicrobial associated colitis (Colitis X), typically associated with *Clostridium difficile*, which may be fatal.

4.4 Special warnings for each target species

Colistin sulfate exerts concentration-dependent activity against Gram-negative bacteria. Following oral administration high concentrations are achieved in the gastrointestinal tract, i.e. the target site, due to the poor absorption of the substance. These factors indicate that a longer duration of treatment than the one indicated in section 4.9, leading to unnecessary exposure, is not recommended.
As an adjunct to treatment, good management and hygiene practices should be introduced in order to reduce the risk of infection and to control the potential build up of resistance.
There is cross-resistance between colistin sulfate and polymyxin B.

4.5 Special precautions for use

Special precautions for use in animals

Use of the product should be based on susceptibility testing and take into account official and local antimicrobials policies.
Colistin sulfate is a last resort drug in human medicine for treatment of infections caused by certain multi-drug resistant bacteria. In order to minimise any potential risk associated with widespread use of colistin sulfate, its use should be limited to treatment or treatment and metaphylaxis of diseases, and should not be used for prophylaxis.
Whenever possible, colistin sulfate should only be used based on susceptibility testing.
An antibiotic with a lower risk of antimicrobial resistance selection (lower AMEG category) should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach.
Use of the product deviating from the instructions given in the SPC may lead to treatment failures and increase the prevalence of bacteria resistant to colistin sulfate.
In the case of newborn animals and animals with severe gastrointestinal and renal disorders, systemic exposure to colistin sulfate may be increased. As a result, neuro- and nephrotoxic effects may occur.
Do not use colistin sulfate as a substitute for good management practices.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

People with known hypersensitivity to polymyxins, such as colistin sulfate, should avoid contact with the veterinary medicinal product.
Avoid direct contact with skin and eyes while handling the product. Personal protective equipment consisting of gloves and protective goggles must be worn while handling and dosing the product.
Do not eat, drink or smoke while handling the product.
Wash splashes from skin immediately with soap and plenty of water.
In case of accidental eye exposure, wash with plenty of water and seek medical attention immediately and show the label to the physician.
If you develop symptoms following exposure such as skin rash, you should seek medical advice and show the physician this warning. Swelling of the face, lips or eyes or difficulty in breathing are more serious symptoms and require urgent medical attention.

Wash hands after use.

4.6 Adverse reactions (frequency and seriousness)

None known.

4.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during pregnancy, lactation or lay. However, colistin sulfate is poorly absorbed after oral administration, therefore the use of colistin sulfate during pregnancy, lactation or lay should not lead to particular problems. Use only according to the benefit-risk assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interaction

After oral administration of colistin sulfate interaction with anaesthetics (curarimimetic agents) and myorelaxants may not be excluded in individual cases. The combination with aminoglycosides and levamisole should be avoided. The effects of colistin sulfate may be antagonized by binary cations (iron, calcium, magnesium) and by unsaturated fatty acids and polyphosphates.

4.9 Amounts to be administered and administration route

Oral use
In drinking water / milk use
Calves, lambs, pigs:100 000 IU of colistin sulfate per kg body weight daily for 3-5 consecutive days in drinking water or milk (replacer) in calves, equivalent to 0.25 ml of the concentrate solution per 10 kg body weight per day for 3-5 days.

Chickens and turkeys: 75 000 IU of colistin sulfate per kg body weight daily for 3-5 consecutive days in drinking water, equivalent to 18.75 ml of the concentrate solution per Ton of body weight per day for 3-5 days.

Duration of treatment should be limited to the minimum time necessary for the treatment of the disease.
Any medicated water which is not consumed within 24 hours should be discarded.
Any medicated milk which is not consumed within 3 hours should be discarded.

Direct oral administration to individual animals
The recommended daily dose should be divided into two if the product is to be administered directly into the mouth of the animal.
Prior to direct oral administration, the product should be diluted with a volume of drinking water equivalent to 2 x the volume of product concentrate to be administered.

Administration via drinking water
The intake of medicated water depends on the clinical condition of the animals. In order to obtain the correct dosage the concentration of colistin sulfate has to be adjusted accordingly. Carefully calculate the average body weight to be treated and the average daily water consumption before each treatment.
Water uptake should be monitored at frequent intervals.

Medicated water should be made every day, immediately prior to provision.
The medicated water should be the only source of drinking water for the animals for the entire duration of the treatment period.

With the following formula, we can calculate an exact dosage:

$$\frac{\text{ml veterinary medicinal product per kg bodyweight and day} \times \text{Average bodyweight (kg) of animals to be treated}}{\text{Average daily water intake (l/animal)}} = \text{ml of veterinary medicinal product per litre of drinking water}$$

• Administration without a dosing pump:
The treatment is distributed in a tank over a period of 24 hours, for 3-5 consecutive days.
The product is added to a volume of the drinking water corresponding to the volume consumed by the animals over the treatment period (24 hours) to achieve a dose of 100 000 IU of colistin sulfate per kg body weight for pigs, lambs and calves and 75 000 IU of colistin sulfate per kg body weight for chickens and turkeys.
• Administration via a dosing pump
The treatment is distributed over a period of 24 hours, for 3-5 consecutive days.
A dosing pump is used to add a stock solution at a pre-determined concentration to the drinking water.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

None.

4.11 Withdrawal period(s)

Cattle (calves), sheep (lambs) and pigs
Meat and offal: 1 day

Chickens and turkeys
Meat and offal: 1 day
Egg: zero days

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Intestinal anti-infectives, antibiotics.
ATCvet code: QA07AA10.

5.1 Pharmacodynamic properties

Colistin sulfate is a polypeptide antibiotic belonging to the class of polymyxins. Colistin sulfate exerts a bactericidal action on susceptible bacterial strains by

disruption of their cytoplasmic membrane, leading to an alteration of the cell permeability and thus to a loss of intracellular material.
Colistin sulfate exhibits a bactericidal effect against a broad spectrum of Gram-negative bacteria among which Enterobacteriaceae, especially *Escherichia coli*.
Colistin sulfate has very little activity against Gram-positive bacteria and fungal organisms.
Colistin sulfate exerts concentration-dependent activity against Gram-negative bacteria.

Gram-positive bacteria, as well as some species of Gram-negative bacteria, such as *Proteus* and *Serratia*, are naturally resistant to colistin sulfate.
Resistance can be caused by chromosomal mutations or can be transferrable (plasmid mediated e.g. mcr genes).

The clinical breakpoints for colistin sulfate (EUCAST, 2021) for Enterobacterales are susceptible ≤ 2 µg/ml and resistant > 2 µg/ml.
The following Minimal Inhibitory Concentrations (MIC) have been determined for colistin in European isolates collected from target species from 2018 to 2019.

Species	Bacterial pathogen	Number of isolates	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)
Chickens	*E. coli*	413	1	1
Turkeys		65	1	1
Pigs		724	1	1
Piglets		118	1	8
Cattle (calves)		418	1	1

Cross resistance has been described between polymyxins.

5.2 Pharmacokinetic particulars

Colistin sulfate is very poorly absorbed from the gastrointestinal tract. Following oral administration high concentrations are achieved in the gastrointestinal tract, i.e. the target site, due to the poor absorption of the substance.
In serum and tissues, the concentrations of colistin are very low. In contrast, it is persistently present and in large quantities in different sections of the digestive tract.
No metabolism was observed.
Colistin sulfate is almost exclusively eliminated in the faeces.

Environmental properties

Colistin is classified as a very persistent substance in soil.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trihydrate sodium acetate
Glacial acetic acid (for pH adjustment)
Benzyl alcohol (E1519)
Glycerol

Purified water

6.2 Major incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 18 months
Shelf life after first opening the immediate packaging: 3 months
Shelf life after dilution in water according to directions: 24 hours
Shelf life after dilution in milk/milk replacer: 3 hours

6.4 Special precautions for storage

Do not store above 25 °C
Protect from light.

6.5 Nature and composition of immediate packaging

The product is presented in 1 L and 5 L white high density polyethylene containers. The containers are sealed by induction and closed by a high density polyethylene screw cap.
Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

SP VETERINARIA S.A.
Crta Reus Vinyols km 4.1
Riudoms (43330)
Spain

8. MARKETING AUTHORISATION NUMBER

Vm 36967/4005

9. DATE OF FIRST AUTHORISATION

29 July 2016

10. DATE OF REVISION OF THE TEXT

September 2021

Approved: 24/09/21